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THE CONCISE GUIDE TO PHARMACOLOGY 2017/18:

Nuclear hormone receptors

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Abstract

The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.13880/full>. Nuclear hormone receptors are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to declare.

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Overview: Nuclear receptors are specialised transcription factors with commonalities of sequence and structure, which bind as homo- or heterodimers to specific consensus sequences of DNA (response elements) in the promoter region of particular target genes. They regulate (either promoting or repressing) transcription of these target genes in response to a variety of endogenous ligands. Endogenous agonists are hydrophobic entities which, when bound to the receptor promote conformational changes in the receptor to allow recruitment (or dissociation) of protein partners, generating a large multiprotein complex.

Two major subclasses of nuclear receptors with identified endogenous agonists can be identified: steroid and non-steroid hormone receptors. Steroid hormone receptors function typically as dimeric entities and are thought to be resident outside the nucleus in the unliganded state in a complex with chaperone proteins, which are liberated upon agonist binding. Migration to the nucleus and interaction with other regulators of gene transcription, including RNA polymerase, acetyltransferases and deacetylases, allows gene transcription to be regulated. Non-steroid hormone receptors typically exhibit a greater distribution

in the nucleus in the unliganded state and interact with other nuclear receptors to form heterodimers, as well as with other regulators of gene transcription, leading to changes in gene transcription upon agonist binding.

Selectivity of gene regulation is brought about through interaction of nuclear receptors with particular consensus sequences of DNA, which are arranged typically as repeats or inverted palindromes to allow accumulation of multiple transcription factors in the promoter regions of genes.

Family structure

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1A. Thyroid hormone receptors

Nuclear hormone receptors → 1A. Thyroid hormone receptors

Overview: Thyroid hormone receptors (TRs, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [41]**) are nuclear hormone receptors of the NR1A family, with diverse roles regulating

macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T₄) and thyroid hormone (triiodothyronine). Once activated by a ligand, the receptor acts as a transcription factor either as a monomer, homodimer or het-

erodimer with members of the retinoid X receptor family. NH-3 has been described as an antagonist at TRs with modest selectivity for TRβ [110].

Nomenclature	Thyroid hormone receptor-α	Thyroid hormone receptor-β
Systematic nomenclature	NR1A1	NR1A2
HGNC, UniProt	THRA, P10827	THRB, P10828
Rank order of potency	triiodothyronine > T ₄	triiodothyronine > T ₄
Agonists	dextrothyroxine [19]	dextrothyroxine [19]
Selective agonists	–	sobetirome [26, 130]

Comments: An interaction with integrin αVβ3 has been suggested to underlie plasma membrane localization of TRs and non-genomic signalling [8]. One splice variant, TRα₂, lacks a functional DNA-binding domain and appears to act as a transcription suppressor. Although radioligand binding assays have been described for these receptors, the radioligands are not commercially available.

Further reading on 1A. Thyroid hormone receptors

Davis PJ *et al.* (2016) Nongenomic actions of thyroid hormone. *Nat Rev Endocrinol* **12**: 111-21 [PMID:26668118]

Elbers LP *et al.* (2016) Thyroid Hormone Mimetics: the Past, Current Status and Future Challenges. *Curr Atheroscler Rep* **18**: 14 [PMID:26886134]

Flamant F *et al.* (2006) International Union of Pharmacology. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. *Pharmacol. Rev.* **58**: 705-11 [PMID:17132849]

Mendoza A *et al.* (2017) New insights into thyroid hormone action. *Pharmacol Ther* **173**: 135-145 [PMID:28174093]

1B. Retinoic acid receptors

Nuclear hormone receptors → 1B. Retinoic acid receptors

Overview: Retinoic acid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [46]**) are nuclear hormone receptors of the NR1B family activated by the vitamin A-derived agonists [tretinoin](#) (ATRA) and [alitretinoin](#), and the RAR-selective synthetic agonists [TTNPB](#) and [adapalene](#). [BMS493](#) is a family-selective antagonist [47].

Nomenclature	Retinoic acid receptor- α	Retinoic acid receptor- β	Retinoic acid receptor- γ
Systematic nomenclature	NR1B1	NR1B2	NR1B3
HGNC, UniProt	RARA , P10276	RARB , P10826	RARG , P13631
Agonists	tretinoin [25]	tretinoin [25]	tretinoin [25]
Sub/family-selective agonists	tazarotene [25]	tazarotene [25], adapalene [24]	tazarotene [25], adapalene [24]
Selective agonists	BMS753 [53], tamibarotene [146], Ro 40-6055 [33]	AC261066 [89], ACS5649 [88, 89]	AHPN [24]
Selective antagonists	Ro 41-5253 (pIC ₅₀ 6.3–7.2) [2, 69]	–	MM 11253 [76]

Comments: [Ro 41-5253](#) has been suggested to be a PPAR γ agonist [129]. [LE135](#) is an antagonist with selectivity for RAR α and RAR β compared with RAR γ [84].

Further reading on 1B. Retinoic acid receptors

Duong V *et al.* (2011) The molecular physiology of nuclear retinoic acid receptors. From health to disease. *Biochim. Biophys. Acta* **1812**: 1023–31 [PMID:20970498]

Germain P *et al.* (2006) International Union of Pharmacology. LX. Retinoic acid receptors. *Pharmacol. Rev.* **58**: 712–25 [PMID:17132850]

Larange A *et al.* (2016) Retinoic Acid and Retinoic Acid Receptors as Pleiotropic Modulators of the Immune System. *Annu Rev Immunol* **34**: 369–94 [PMID:27168242]

Saeed A *et al.* (2017) The interrelationship between bile acid and vitamin A homeostasis. *Biochim Biophys Acta* **1862**: 496–512 [PMID:28111285]

1C. Peroxisome proliferator-activated receptors

Nuclear hormone receptors → 1C. Peroxisome proliferator-activated receptors

Overview: Peroxisome proliferator-activated receptors (PPARs, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [101]**) are nuclear hormone receptors of the NR1C family, with diverse roles regulating lipid homeostasis, cellular differentiation, proliferation and the immune response. PPARs have many potential endogenous agonists [13, 101], including [15-deoxy- \$\Delta^{12,14}\$ -PGJ₂](#), prosta-

cyclin ([PGI₂](#)), many fatty acids and their oxidation products, lysophosphatidic acid (LPA) [98], [13-HODE](#), [15S-HETE](#), [Paz-PC](#), [azelaoyl-PAF](#) and leukotriene B₄ (LTB₄). [Bezafibrate](#) acts as a non-selective agonist for the PPAR family [155]. These receptors also bind hypolipidaemic drugs (PPAR α) and anti-diabetic thiazolidinediones (PPAR γ), as well as many non-steroidal anti-inflammatory drugs, such as [sulindac](#) and [indomethacin](#). Once

activated by a ligand, the receptor forms a heterodimer with members of the retinoid X receptor family and can act as a transcription factor. Although radioligand binding assays have been described for all three receptors, the radioligands are not commercially available. Commonly, receptor occupancy studies are conducted using fluorescent ligands and truncated forms of the receptor limited to the ligand binding domain.

Nomenclature	Peroxisome proliferator-activated receptor- α	Peroxisome proliferator-activated receptor- β/δ	Peroxisome proliferator-activated receptor- γ
Systematic nomenclature	NR1C1	NR1C2	NR1C3
HGNC, UniProt	PPARA , Q07869	PPARD , Q03181	PPARG , P37231
Selective agonists	GW7647 [17, 18], CP-775146 [67], pirinixic acid [155], gemfibrozil [31]	GW0742X [50, 148], GW501516 [112]	GW1929 [17], bardoxolone (Partial agonist) [149], rosiglitazone [59, 80, 86, 161], troglitazone [59, 161], pioglitazone [7, 59, 127, 161], ciglitazone [59]
Selective antagonists	GW6471 (pIC ₅₀ 6.6) [158]	GSK0660 (pIC ₅₀ 6.5) [131]	T0070907 (pK _i 9) [77], GW9662 (Irreversible inhibition) (pIC ₅₀ 8.1) [78], CDDO-Me (pK _i 6.9) [149]

Comments: As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (*e.g.* [12, 109, 124]). Agonists with mixed activity at PPAR α and PPAR γ have also been described (*e.g.* [35, 52, 159]).

Further reading on 1C. Peroxisome proliferator-activated receptors

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 Gross B *et al.* (2017) PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol* **13**: 36–49 [PMID:27636730]
 Hallenborg P *et al.* (2016) The elusive endogenous adipogenic PPARgamma agonists: Lining up the suspects. *Prog Lipid Res* **61**: 149–62 [PMID:26703188]

Michalik L *et al.* (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacol. Rev.* **58**: 726–41 [PMID:17132851]
 Sauer S. (2015) Ligands for the Nuclear Peroxisome Proliferator-Activated Receptor Gamma. *Trends Pharmacol Sci* **36**: 688–704 [PMID:26435213]

1D. Rev-Erb receptors

Nuclear hormone receptors → 1D. Rev-Erb receptors

Overview: Rev-erb receptors (nomenclature as agreed by the [NC-IUPHAR Subcommittee on Nuclear Hormone Receptors](#) [6]) have yet to be officially paired with an endogenous ligand, but are thought to be activated by heme.

Nomenclature	Rev-Erb- α	Rev-Erb- β
Systematic nomenclature	NR1D1	NR1D2
HGNC, UniProt	NR1D1 , P20393	NR1D2 , Q14995
Endogenous agonists	heme [121, 160]	heme [97, 121, 160]
Selective agonists	GSK4112 [51], GSK4112 [70]	–
Selective antagonists	SR8278 (pIC ₅₀ 6.5) [70]	–

Further reading on 1D. Rev-Erb receptors

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798-836 [PMID:17132856]
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Gonzalez-Sanchez E *et al.* (2015) Nuclear receptors in acute and chronic cholestasis. *Dig Dis* **33**: 357-66 [PMID:26045270]
Sousa EH *et al.* (2017) Drug discovery targeting heme-based sensors and their coupled activities. *J Inorg Biochem* **167**: 12-20 [PMID:27893989]

1F. Retinoic acid-related orphans

Nuclear hormone receptors → 1F. Retinoic acid-related orphans

Overview: Retinoic acid receptor-related orphan receptors (ROR, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be assigned a definitive endogenous ligand, although RORα may be synthesized with a ‘captured’ agonist such as [cholesterol](#) [65, 66].

Nomenclature	RAR-related orphan receptor-α	RAR-related orphan receptor-β	RAR-related orphan receptor-γ
Systematic nomenclature	NR1F1	NR1F2	NR1F3
HGNC, UniProt	RORA , P35398	RORB , Q92753	RORC , P51449
Endogenous agonists	cholesterol [66, 114]	–	–
Selective agonists	7-hydroxycholesterol [14], cholesterol sulphate [14, 66]	–	–

Comments: [tretinoin](#) shows selectivity for RORβ within the ROR family [136]. RORα has been suggested to be a nuclear receptor responding to [melatonin](#) [154].

Further reading on 1F. Retinoic acid-related orphans

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798-836 [PMID:17132856]
Guillemot-Legris O *et al.* (2016) Oxysterols in Metabolic Syndrome: From Bystander Molecules to Bioactive Lipids. *Trends Mol Med* **22**: 594-614 [PMID:27286741]
Cyr P *et al.* (2016) Recent progress on nuclear receptor RORgamma modulators. *Bioorg Med Chem Lett* **26**: 4387-93 [PMID:27542308]
Mutemberezi V *et al.* (2016) Oxysterols: From cholesterol metabolites to key mediators. *Prog Lipid Res* **64**: 152-169 [PMID:27687912]
Dahlman-Wright K *et al.* (2006) Overview of nomenclature of nuclear receptors. *Pharmacol Rev* **58**: 685-704 [PMID:17132848]

1H. Liver X receptor-like receptors

Nuclear hormone receptors → 1H. Liver X receptor-like receptors

Overview: Liver X and farnesoid X receptors (LXR and FXR, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [105]**) are members of a steroid analogue-activated nuclear receptor subfamily, which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXRs appear to be activated by bile acids.

Nomenclature	Farnesoid X receptor	Farnesoid X receptor-β	Liver X receptor-α	Liver X receptor-β
Systematic nomenclature	NR1H4	NR1H5	NR1H3	NR1H2
HGNC, UniProt	NR1H4 , Q96R11	NR1H5P , –	NR1H3 , Q13133	NR1H2 , P55055
Potency order	chenodeoxycholic acid > lithocholic acid, deoxycholic acid [92, 115]	–	20S-hydroxycholesterol, 22R-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [79]	20S-hydroxycholesterol, 22R-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [79]
Endogenous agonists	–	lanosterol [113] – Mouse	–	–
Selective agonists	GW4064 [94], obeticholic acid [116], fexaramine [36]	–	–	–
Selective antagonists	guggulsterone (pIC ₅₀ 5.7–6) [157]	–	–	–

Comments: [T0901317](#) [122] and [GW3965](#) [27] are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity.

Further reading on 1H. Liver X receptor-like receptors

Courtney R *et al.* (2016) LXR Regulation of Brain Cholesterol: From Development to Disease. *Trends Endocrinol Metab* **27**: 404–14 [PMID:27113081]

Gadaleta RM *et al.* (2017) Bile acids and colon cancer: Is FXR the solution of the conundrum? *Mol Aspects Med* [PMID:28400119]

Merlen G *et al.* (2017) Bile acids and their receptors during liver regeneration: "Dangerous protectors". *Mol Aspects Med* [PMID:28302491]

Moore DD *et al.* (2006) International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnane X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. *Pharmacol Rev* **58**: 742–59 [PMID:17132852]

Mouzat K *et al.* (2016) Liver X receptors: from cholesterol regulation to neuroprotection—a new barrier against neurodegeneration in amyotrophic lateral sclerosis? *Cell Mol Life Sci* **73**: 3801–8 [PMID:27510420]

Schulman IG. (2017) Liver X receptors link lipid metabolism and inflammation. *FEBS Lett* [PMID:28555747]

1I. Vitamin D receptor-like receptors

Nuclear hormone receptors → 1I. Vitamin D receptor-like receptors

Overview: Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [105]**) are members of the NR11 family of nuclear receptors, which form heterodimers with members of the retinoid X receptor family. PXR and CAR are activated by a range of exogenous compounds, with no established endogenous physiological agonists, although high concentrations of bile acids and bile pigments activate PXR and CAR [105].

Nomenclature	Vitamin D receptor	Pregnane X receptor	Constitutive androstane receptor
Systematic nomenclature	NR111	NR112	NR113
HGNC, UniProt	VDR , P11473	NR112 , O75469	NR113 , Q14994
Endogenous agonists	1,25-dihydroxyvitamin D3 [11, 39]	17 β -estradiol [64]	–
Selective agonists	seocalcitol [28, 153], doxercalciferol	hyperforin [106, 152], 5β-pregnane-3,20-dione [64], lovastatin [81], rifampicin [15, 81]	TCPOBOP [144] – Mouse, CITCO [91]
Selective antagonists	TEI-9647 (pIC ₅₀ 8.2) [126] – Chicken, ZK159222 (pIC ₅₀ 7.5) [42, 60]	–	–
Comments	–	–	clotrimazole [107] and T0901317 [68] although acting at other sites, function as antagonists of the constitutive androstane receptor.

Further reading on 1I. Vitamin D receptor-like receptors

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798–836 [PMID:17132856]
 Long MD *et al.* (2015) Vitamin D receptor and RXR in the post-genomic era. *J Cell Physiol.* **230**: 758–66 [PMID:25335912]

Moore DD *et al.* (2006) International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnane X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. *Pharmacol. Rev.* **58**: 742–59 [PMID:17132852]

2A. Hepatocyte nuclear factor-4 receptors

Nuclear hormone receptors → 2A. Hepatocyte nuclear factor-4 receptors

Overview: The nomenclature of hepatocyte nuclear factor-4 receptors is agreed by the **NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**. While linoleic acid has been identified as the endogenous ligand for HNF4 α its function remains ambiguous [163]. HNF4 γ has yet to be paired with an endogenous ligand.

Nomenclature	Hepatocyte nuclear factor-4-α	Hepatocyte nuclear factor-4-γ
Systematic nomenclature	NR2A1	NR2A2
HGNC, UniProt	HNF4A , P41235	HNF4G , Q14541
Endogenous agonists	linoleic acid [163]	–
Selective antagonists	BI6015 [71]	–
Comments	HNF4 α has constitutive transactivation activity [163] and binds DNA as a homodimer [63].	

Further reading on 2A. Hepatocyte nuclear factor-4 receptors

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798-836 [PMID:17132856]
 Germain P *et al.* (2006) Overview of nomenclature of nuclear receptors. *Pharmacol. Rev.* **58**: 685-704 [PMID:17132848]
 Garattini E *et al.* (2016) Lipid-sensors, enigmatic-orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. *Oncotarget* **7**: 42661-42682 [PMID:26894976]

Lu H. (2016) Crosstalk of HNF4 α with extracellular and intracellular signaling pathways in the regulation of hepatic metabolism of drugs and lipids. *Acta Pharm Sin B* **6**: 393-408 [PMID:27709008]
 Walesky CE *et al.* (2015) Role of hepatocyte nuclear factor 4 α (HNF4 α) in cell proliferation and cancer. *Gene Expr* **16**: 101-8 [PMID:25700366]

2B. Retinoid X receptors

[Nuclear hormone receptors](#) → [2B. Retinoid X receptors](#)

Overview: Retinoid X receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [45]**) are NR2B family members activated by [alitretinoin](#) and the RXR-selective agonists [bexarotene](#) and [LG100268](#), sometimes referred to as rexinoids. [UVI3003](#) [108] and [HX 531](#) [37] have been described as a pan-RXR antagonists. These receptors form RXR-RAR heterodimers and RXR-RXR homodimers [22, 96].

Nomenclature	Retinoid X receptor-α	Retinoid X receptor-β	Retinoid X receptor-γ
Systematic nomenclature	NR2B1	NR2B2	NR2B3
HGNC, UniProt	RXRA , P19793	RXRB , P28702	RXRG , P48443
Sub/family-selective agonists	bexarotene [16, 21, 141]	bexarotene [16, 21, 141]	bexarotene [16, 21, 141]
Selective agonists	CD3254 [48]	–	–

Further reading on 2B. Retinoid X receptors

Germain P *et al.* (2006) International Union of Pharmacology. LXIII. Retinoid X receptors. *Pharmacol. Rev.* **58**: 760–72 [PMID:17132853]
Long MD *et al.* (2015) Vitamin D receptor and RXR in the post-genomic era. *J Cell Physiol* **230**: 758–66 [PMID:25335912]

Menendez-Gutierrez MP *et al.* (2017) The multi-faceted role of retinoid X receptor in bone remodeling. *Cell Mol Life Sci* **74**: 2135–2149 [PMID:28105491]

2C. Testicular receptors

Nuclear hormone receptors → 2C. Testicular receptors

Overview: Testicular receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand, although testicular receptor 4 has been reported to respond to retinoids.

Nomenclature	Testicular receptor 2	Testicular receptor 4
Systematic nomenclature	NR2C1	NR2C2
HGNC, UniProt	NR2C1, P13056	NR2C2, P49116
Endogenous agonists	–	retinol [169], tretinoin [169]
Comments	Forms a heterodimer with TR4; gene disruption appears without effect on testicular development or function [132].	Forms a heterodimer with TR2.

Further reading on 2C. Testicular receptors

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798–836 [PMID:17132856]
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Wu D *et al.* (2016) The emerging roles of orphan nuclear receptors in prostate cancer. *Biochim. Biophys. Acta* **1866**: 23–36 [PMID:27264242]

2E. Tailless-like receptors

Nuclear hormone receptors → 2E. Tailless-like receptors

Overview: Tailless-like receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	TLX	PNR
Systematic nomenclature	NR2E1	NR2E3
HGNC, UniProt	NR2E1 , Q9Y466	NR2E3 , Q9Y5X4
Comments	Gene disruption is associated with abnormal brain development [75 , 104].	–

Further reading on 2E. Tailless-like receptors

- Benod C *et al.* (2016) TLX: An elusive receptor. *J. Steroid Biochem. Mol. Biol.* **157**: 41-7 [[PMID:26554934](#)]
 Germain P *et al.* (2006) Overview of nomenclature of nuclear receptors. *Pharmacol. Rev.* **58**: 685-704 [[PMID:17132848](#)]
 Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798-836 [[PMID:17132856](#)]

2F. COUP-TF-like receptors

Nuclear hormone receptors → 2F. COUP-TF-like receptors

Overview: COUP-TF-like receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [[6](#)]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	COUP-TF1	COUP-TF2	V-erbA-related gene
Systematic nomenclature	NR2F1	NR2F2	NR2F6
HGNC, UniProt	NR2F1 , P10589	NR2F2 , P24468	NR2F6 , P10588
Comments	Gene disruption is perinatally lethal [120].	Gene disruption is embryonically lethal [117].	Gene disruption impairs CNS development [151].

Further reading on 2F. COUP-TF-like receptors

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3B. Estrogen-related receptors

Nuclear hormone receptors → 3B. Estrogen-related receptors

Overview: Estrogen-related receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	Estrogen-related receptor- α	Estrogen-related receptor- β	Estrogen-related receptor- γ
Systematic nomenclature	NR3B1	NR3B2	NR3B3
HGNC, UniProt	ESRRA , P11474	ESRRB , O95718	ESRRG , P62508
Comments	Activated by some dietary flavonoids [138]; activated by the synthetic agonist GSK4716 [181] and blocked by XCT790 [156].	May be activated by DY131 [162].	May be activated by DY131 [162].

Further reading on 3B. Estrogen-related receptors

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4A. Nerve growth factor IB-like receptors

Nuclear hormone receptors → 4A. Nerve growth factor IB-like receptors

Overview: Nerve growth factor IB-like receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	Nerve Growth factor IB	Nuclear receptor related 1	Neuron-derived orphan receptor 1
Systematic nomenclature	NR4A1	NR4A2	NR4A3
HGNC, UniProt	NR4A1 , P22736	NR4A2 , P43354	NR4A3 , Q92570
Comments	An endogenous agonist, cytosporone B , has been described [164], although structural analysis and molecular modelling has not identified a ligand binding site [4 , 40 , 150].	–	–

Further reading on 4A. Nerve growth factor IB-like receptors

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5A. Fushi tarazu F1-like receptors

Nuclear hormone receptors → 5A. Fushi tarazu F1-like receptors

Overview: Fushi tarazu F1-like receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	Steroidogenic factor 1	Liver receptor homolog-1
Systematic nomenclature	NR5A1	NR5A2
HGNC, UniProt	NR5A1 , Q13285	NR5A2 , O00482
Comments	Reported to be inhibited by AC45594 [32] and SID7969543 [90].	–

Further reading on 5A. Fushi tarazu F1-like receptors

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6A. Germ cell nuclear factor receptors

Nuclear hormone receptors → 6A. Germ cell nuclear factor receptors

Overview: Germ cell nuclear factor receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	Germ cell nuclear factor
Systematic nomenclature	NR6A1
HGNC, UniProt	NR6A1, Q15406

Further reading on 6A. Germ cell nuclear factor receptors

Benoit G *et al.* (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol. Rev.* **58**: 798-836 [PMID:17132856]
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0B. DAX-like receptors

Nuclear hormone receptors → 0B. DAX-like receptors

Overview: Dax-like receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]**) have yet to be officially paired with an endogenous ligand.

Nomenclature	DAX1	SHP
Systematic nomenclature	NR0B1	NR0B2
HGNC, UniProt	NR0B1, P51843	NR0B2, Q15466

Further reading on OB. DAX-like receptors

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Steroid hormone receptors

Nuclear hormone receptors → Steroid hormone receptors

Overview: Steroid hormone receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [30, 87]**) are nuclear hormone receptors of the NR3 class, with endogenous agonists that may be divided into 3-hydroxysteroids (**estrone** and **17β-estradiol**) and 3-ketosteroids (**dihydrotestosterone** [DHT], **aldosterone**, **cortisol**, **corticosterone**, **progesterone** and **testosterone**). These receptors exist as dimers coupled with chaperone molecules (such as **hsp90β** (**HSP90AB1**, **P08238**) and immunophilin FKBP52:**FKBP4**, **Q02790**), which are shed on binding the steroid hormone. Al-

though rapid signalling phenomena are observed [83, 119], the principal signalling cascade appears to involve binding of the activated receptors to nuclear hormone response elements of the genome, with a 15-nucleotide consensus sequence AGAA-CAnnnTGTCT (*i.e.* an inverted palindrome) as homo- or heterodimers. They also affect transcription by protein-protein interactions with other transcription factors, such as activator protein 1 (AP-1) and nuclear factor κB (NF-κB). Splice variants of each of these receptors can form functional or non-functional monomers that can dimerize to form functional or

non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce functional AA, AB and BB receptors with distinct characteristics [145]. A 7TM receptor responsive to estrogen (**GPER1**, **Q99527**, also known as GPR30, see [118]) has been described. Human orthologues of 7TM 'membrane progesterin receptors' (**PAQR7**, **PAQR8** and **PAQR5**), initially discovered in fish [170, 171], appear to localize to intracellular membranes and respond to 'non-genomic' progesterone analogues independently of G proteins [134].

3A. Estrogen receptors

Nuclear hormone receptors → Steroid hormone receptors → 3A. Estrogen receptors

Overview: Estrogen receptor (ER) activity regulates diverse physiological processes *via* transcriptional modulation of target genes. The selection of target genes and the magnitude of the response, be it induction or repression, are determined by many factors, including the effect of the hormone ligand and DNA binding on ER structural conformation, and the local cellular regulatory environment. The cellular environment defines the specific complement of DNA enhancer and promoter elements present and the availability of coregulators to form functional transcription complexes. Together, these determinants control the resulting biological response.

Nomenclature	Estrogen receptor-α	Estrogen receptor-β
Systematic nomenclature	NR3A1	NR3A2
HGNC, UniProt	ESR1, P03372	ESR2, Q92731
Endogenous agonists	estriol [74], estrone [74]	–

(continued)		
Nomenclature	Estrogen receptor- α	Estrogen receptor- β
Selective agonists	propylpyrazone [73, 135], ethinylestradiol [62]	WAY200070 [93], diarylpropionitrile [100, 135], prinaberal [29, 93]
Sub/family-selective antagonists	bazedoxifene (pIC ₅₀ 7.6) [103]	bazedoxifene (pIC ₅₀ 7.1) [103]
Selective antagonists	clomiphene (pK _i 8.9) [3], methyl-piperidino-pyrazole (pK _i 8.6) [139]	R,R-THC (pK _i 8.4) [99, 140], PHTPP (pK _i 6.9) [168]

Comments: R,R-THC exhibits partial agonist activity at ER α [99, 140]. Estrogen receptors may be blocked non-selectively by [tamoxifen](#) and [raloxifene](#) and labelled by [³H]17 β -estradiol and [³H]tamoxifen. Many agents thought initially to be antagonists at estrogen receptors appear to have tissue-specific efficacy (*e.g.* [Tamoxifen](#) is an antagonist at estrogen receptors in the breast, but is an agonist at estrogen receptors in the uterus), hence the descriptor SERM (selective estrogen receptor modulator) or SnuRM (selective nuclear receptor modulator). [Y134](#) has been suggested to be an ER α -selective estrogen receptor modulator [111].

Further reading on 3A. Estrogen receptors

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3C. 3-Ketosteroid receptors

Nuclear hormone receptors → Steroid hormone receptors → 3C. 3-Ketosteroid receptors

Nomenclature	Androgen receptor	Glucocorticoid receptor
Systematic nomenclature	NR3C4	NR3C1
HGNC, UniProt	AR, P10275	NR3C1, P04150
Rank order of potency	dihydrotestosterone [142] > testosterone	cortisol, corticosterone >> aldosterone, deoxycortisone [125]
Selective agonists	testosterone propionate [95], mibolerone [49], fluoxymesterone [61], methyltrienolone [148], dromostanolone propionate	fluticasone propionate [10], beclomethasone [3], methylprednisolone [3], fluocinonide [3], betamethasone [3], budesonide [102]
Selective antagonists	bicalutamide (pK _i 7.7) [70], PF0998425 (pIC ₅₀ 7.1–7.5) [85], enzalutamide (pIC ₅₀ 7.4) [143], nilutamide (pIC ₅₀ 7.1–7.1) [133], hydroxyflutamide (pEC ₅₀ 6.6) [148], galeterone (pIC ₅₀ 6.4) [56], flutamide (pK _i 5.4) [147]	onapristone (pIC ₅₀ 7.6) [165], ZK112993
Labelled ligands	[³ H]dihydrotestosterone (Selective Agonist), [³ H]methyltrienolone (Selective Agonist), [³ H]mibolerone (Agonist)	[³ H]dexamethasone (Agonist)

Nomenclature	Mineralocorticoid receptor	Progesterone receptor
Systematic nomenclature	NR3C2	NR3C3
HGNC, UniProt	NR3C2 , P08235	PGR , P06401
Rank order of potency	corticosterone , cortisol , aldosterone [58, 125], progesterone [125]	progesterone [38]
Selective agonists	–	medroxyprogesterone (Affinity at human PR-A) [166], ORG2058 , levonorgestrel [9, 128]
Selective antagonists	finerenone (pIC ₅₀ 7.7) [20], eplerenone (pK _i 6.9) [5], onapristone (pIC ₅₀ 6.3) [165], RU28318 , ZK112993	ulipristal acetate (pIC ₅₀ 9.7) [123], mifepristone (Mixed) (pK _i 9) [167], onapristone (pK _i 7.7) [54], ZK112993
Labelled ligands	[³H]aldosterone (Selective Agonist) [44, 137] – Rat	[³H]ORG2058 (Selective Agonist)

Comments: [\[³H\]dexamethasone](#) also binds to MR *in vitro*. PR antagonists have been suggested to subdivide into Type I (*e.g.* [onapristone](#)) and Type II (*e.g.* [ZK112993](#)) groups. These groups appear to promote binding of PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to a transcription-neutral complex [43, 82]. Mutations in AR underlie testicular feminization and androgen insensitivity syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

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